

In the Specification:

Please amend the specification as shown.

Please amend the paragraph on page 5, line 33, to page 6, line 2, as follows:

Figure 2 illustrates potency and specificity of LNA oligomeric compounds in an in vitro system. The LNA 16-mers shows effective down regulation, much better than the phosphorothioate 20-mer. The LNA oligomeric compounds also shows good specificity, compared to the compounds containing 6 mismatches. (The 4% given in *italic* have a 28S background smear. This leads to an overestimate of the 28S signal intensity. Therefore the %mRNA is put in brackets on the left side and not corrected for the RNA loading (i.e. the 28S signal). The Cur 219 and Cur 2120 oligonucleotides are shown in SEQ ID NOS 88-89, respectively.

Please amend the paragraph on page 6, lines 4-6, as follows:

Figure 3 shows tumor growth reduction by the oligomeric compound Cur2524 (LNA-gapmer). It is also shown that the iso-sequential 16-mer phosphorothioate and the mismatch control did not have any effect. The Cur 2522, Cur 2131 and Cur 2132 oligonucleotides are shown in SEQ ID NOS 90-92, respectively.

Please amend the paragraph on page 13, lines 19-35, as follows:

Preferred oligomeric compounds comprises at least a 8-nucleobase portion, said subsequence being selected from SEQ ID NO 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 76, 77 or 79 and their sequences are presented in table 1 (SEQ ID NOS 93-

134), 3 (SEQ ID NOS 75, 135 and 76) and 4 (SEQ ID NOS 77 & 137). The oligomeric compounds according to the invention are potent modulators of target. For example, in vitro inhibition of target is shown in Table 1 measured by Real time PCR. Figure 2 shows in vitro potency and specificity of oligomeric compounds according to the invention measured by Northern Blot. Very low IC50 of oligomeric compounds is shown in table 2 (compared to the previously reported IC50, see section "Background of the invention"). The compound of the invention also induces apoptosis (Figure 6). In vivo specificity and potency of oligomeric compounds are shown in Figure 3. Furthermore, in vivo superiority of a short oligomeric compound compared to a traditional long antisense compound is shown Figure 4. Figure 9 show in vivo potency of 2 compounds of the invention. All the above-mentioned experimental observations show that the compounds according to the invention can constitute the active compound in a pharmaceutical composition.

Please amend the paragraph on page 14, lines 8-19, as follows:

In another embodiment of the invention, said nucleosides are linked to each other by means of a phosphorothioate group. An interesting embodiment of the invention is directed to compounds of SEQ NO 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74 and 75 wherein each linkage group within each compound is a phosphorothioate group. Such modifications is denoted by the subscript S. Alternatively stated, one aspect of the invention is directed to compounds of SEQ NOS 2_{A5}, 3_{A5}, 4_{A5}, 5_{A5}, 6_{A5}, 7_{A5}, 8_{A5}, 9_{A5}, 10_{A5}, 11_{A5}, 12_{A5}, 13_{A5}, 14_{A5}, 15_{A5}, 16_{A5}, 17_{A5}, 18_{A5}, 19_{A5}, 20_{A5}, 21_{A5}, 22_{A5}, 23_{A5}, 24_{A5}, 25_{A5}, 26_{A5}, 27_{A5}, 28_{A5}, 29_{A5}, 30_{A5}, 31_{A5}, 32_{A5}, 33_{A5}, 34_{A5}, 35_{A5}, 36_{A5}, 37_S, 38_{A5}, 39_{A5}, 40_{A5}, 41_{A5}, 42_{A5}, 43_{A5}, 44_{A5}, 45_{A5}, 46_{A5}, 47_{A5}, 48_{A5}, 49_{A5}, 50_{A5}, 51_{A5}, 52_{A5}, 53_{A5}, 54_{A5}, 55_{A5}, 56_{A5}, 57_{A5}, 58_{A5}, 59_{A5}, 60_{A5}, 61_{A5}, 62_{A5}, 63_{A5}, 64_{A5}, 65_{A5}, 66_{A5}, 67_{A5}, 68_{A5}, 69_{A5}, 70_{A5}, 71_{A5}, 72_{A5}, 73_{A5}, 74_A and 75_A, 93, 96, 99, 102, 105, 108, 111, 114, 117, 120, 123, 126, 129, 132 and 142-201.

Please amend the paragraph on page 14, lines 21-25, as follows:

A further aspect of the invention is directed to compounds of SEQ NOS ~~2_B, 3_B, 4_B, 5_B, 6_S, 7_S, 8_B, 9_B, 10_B, 11_B, 12_B, 13_B, 14_B, 15_B, 16_B, 17_B, 18_B, 19_B, 20_B, 21_B, 22_B, 23_B, 24_B, 25_B, 26_B, 27_B, 28_B, 29_B, 30_B, 31_B, 32_B, 33_B, 34_B, 35_B, 36_B, 37_S, 38_B, 39_B, 40_B, 41_B, 42_B, 43_B, 44_B, 45_B, 46_B, 47_B, 48_B, 49_B, 50_B, 51_B, 52_B, 53_B, 54_B, 55_B, 56_B, 57_B, 58_B, 59_B, 60_B, 61_B, 62_B, 63_B, 64_B, 65_B, 66_B, 67_B, 68_B, 69_B, 70_B, 71_B, 72_B, 73_B, 74_B and 75_B~~ 94, 97, 100, 103, 106, 109, 112, 115, 118, 121, 124, 127, 130, 133, 135 and 140.

Please amend the paragraph on page 14, lines 27-31, as follows:

A further aspect of the invention is directed to compounds of SEQ NOS ~~2_C, 3_C, 4_C, 5_C, 6_S, 7_S, 8_C, 9_C, 10_C, 11_C, 12_C, 13_C, 14_C, 15_C, 16_C, 17_C, 18_C, 19_C, 20_C, 21_C, 22_C, 23_C, 24_C, 25_C, 26_C, 27_C, 28_C, 29_C, 30_C, 31_C, 32_C, 33_C, 34_C, 35_C, 36_C, 37_S, 38_C, 39_C, 40_C, 41_C, 42_C, 43_C, 44_C, 45_C, 46_C, 47_C, 48_C, 49_C, 50_C, 51_C, 52_C, 53_C, 54_C, 55_C, 56_C, 57_C, 58_C, 59_C, 60_C, 61_C, 62_C, 63_C, 64_C, 65_C, 66_C, 67_C, 68_C, 69_C, 70_C, 71_C, 72_C, 73_C, 74_C and 75_C~~ 95, 98, 101, 104, 107, 110, 113, 116, 119, 122, 125, 128, 131 and 134.

Please amend the paragraph on page 44, line 35, to page 45, line 6, as follows:

First strand synthesis

First strand synthesis was performed using OmniScript Reverse Transcriptase kit (cat# 205113, Qiagen) according to the manufacturers instructions.

For each sample 0.5 μ g total RNA was adjusted to 12 μ l each with RNase free H₂O and mixed with 2 μ l poly (dT)₁₂₋₁₈ (SEQ ID NO: 141)(2.5 μ g/ml) (Life Technologies, GibcoBRL,

Roskilde, DK), 2 μ l dNTP mix (5 mM each dNTP), 2 μ l 10x Buffer RT, 1 μ l RNAGuard™Rnase INHIBITOR (33.3U/ml), (cat# 27-0816-01, Amersham Pharmacia Biotech, Hørsholm, DK) and 1 μ l OmniScript Reverse Transcriptase (4 U/ μ l) followed by incubation at 37°C for 60 minutes and heat inactivation of the enzyme at 93°C for 5 minutes.

Please amend the paragraph on page 45, line 38, to page 46, line 4, as follows:

For human Ha-ras the PCR primers were:

forward primer: 5' gccggatgcaggaaggag 3' (SEQ ID NO: 78)(final concentration in the assay; 0.3 μ M reverse primer: 5' gtccagcagcccttcctt 3' (SEQ ID NO: 79) (final concentration in the assay; 0.3 μ M)(SEQ ID NO: 81) and the PCR probe was: 5' FAM-cgtccttcctcctcctcctccgtctg -TAMRA 3'(SEQ ID NO: 80) (final concentration in the assay; 0.1 μ M)

Please amend the paragraph on page 46, lines 13-17, as follows:

For quantification of mouse GAPDH mRNA the following primers and probes were designed: Sense primer 5'aaggctgtgggaaggtcatc 3' (SEQ ID NO: 81) (0.3 μ M final concentration), antisense primer 5' gtcagatccacgacggacacatt (SEQ ID NO: 82) (0.6 μ M final concentration), TaqMan probe 5' FAM-gaagctcactggcatggcatggcctccgtgttc-TAMRA 3' (SEQ ID NO: 83) (0.2 μ M final concentration).

Please amend the paragraph on page 46, lines 31, to page 47, line 2, as follows:

Example 8: in vitro analysis: Northern Blot Analysis of Ha-ras mRNA Levels

Northern blot analysis was carried out by procedures well known in the art essentially as described in Current Protocols in Molecular Biology, John Wiley & Sons.

The hybridisation probe was obtained by PCR-amplification of a 381 bp fragment from 15PC3 cDNA obtained by reverse transcription PCR as described in example 8. The reaction was carried out using primers 5' aatctcggcaggctcaggac 3' (SEQ ID NO: 84) (forward) and 5' gggatgttcaagacagtctgtgc 3' (SEQ ID NO: 85) (reverse) at 0,5 μ M final concentration each, 200 nM each dNTP, 1,5 mM $MgCl_2$ and Platinum Taq DNA polymerase (Invitrogen cat. no. 10966-018). The DNA was amplified for 40 cycles on a Perkin Elmer 9700 thermocycler using the following program: 94°C for 2 min. then 40 cycles of 94°C for 30 sec. and 72°C for 30 sec. with a decrease of 0.5°C per cycle followed by 72°C for 7 min.

Please amend the paragraph on page 47, lines 31, to page 47, line 2, as follows:

Equality of RNA sample loading was assessed by stripping the blot in 0,5% SDS in H_2O at 85°C and reprobing with a labelled GAPDH (glyceraldehyde-3-phosphate dehydrogenase) probe obtained essentially as described above using the primers 5' aac gga ttg ggt cgt att 3' (SEQ ID NO: 86)(forward) and 5' taa gca gtt ggt ggt gca 3' (SEQ ID NO: 87) (reverse).

Please amend Table 1 starting on page 50, as follows:

SEQ ID NO	Target site	Oligomeric compound Sequence 5'-3'	Internal NO & ID NO +Design NO	Specific design of Oligomeric compound Capital letters bold β -D-oxy-LNA S= phosphorthioate O= -O-P(O) ₂ -O- Small letters DNA sugar	% Inhibition at 25 nM oligo
2	1742 (260 K-ras)	ATTCGTCCACAAAA TG	CUR270 9 2A 93	A _S T _S T _S C _S G _S T _S C _S C _S a _S C _S a _S a _S A _S A _S T _S G	29
			2B 94	A _S T _S T _S C _S G _S T _S C _S C _S a _S C _S a _S A _S A _S T _S G	
			2C 95	A _O T _O T _O C _O G _S T _S C _S C _S a _S C _S a _S A _O A O _T O _G	
3	1733 (323 N-ras)	CAAAATGGTTCTGG AT	CUR271 0 3A 96	C _S A _S A _S A _S a _S t _S G _S G _S T _S C _S T _S G _S G _S A _S T	60
			3B 97	C _S A _S A _S A _S a _S t _S G _S G _S T _S C _S T _S G _S G _S A _S t	
			3C 98	C _O A _O A _O A _O a _S t _S G _S G _S T _S C _S T _S G _O G _O A _O T	
4	1745 (263 K-ras)	CGTATTCGTCCACA AA	CUR271 1 4A 99	C _S G _S T _S A _S t _S C _S G _S T _S C _S C _S a _S C _S A _S A _S A	67
			4B 100	C _S G _S T _S A _S t _S C _S G _S T _S C _S C _S a _S C _S A _S A _S a	
			4C 101	C _O G _O T _O A _O t _S C _S G _S T _S C _S C _S a _S C _O A _O A _O A	
5	2158	CACACACAGGAAG CCC	CUR271 2 5A 102	C _S A _S C _S A _S C _S a _S C _S a _S G _S G _S a _S A _S G _S C _S C _S C	62
			5B 103	C _S A _S C _S A _S C _S a _S C _S a _S G _S G _S a _S A _S G _S C _S C _S c	

			5C <u>104</u>	C _O A _O C _O A _O c _s a _s c _s a _s g _s g _s a _s a _s G _O C O _C O _C	
6	3701	CCCATCTGTGCCCCG AC	CUR271 3 6A <u>105</u>	C _s C _s C _s A _s t _s c _s t _s g _s t _s g _s c _s c _s C _s G _s A _s C	90
			6B <u>106</u>	C _s C _s C _s A _s t _s c _s t _s g _s t _s g _s c _s c _s C _s G _s A _s vc	
			6C <u>107</u>	C _O C _O C _O A _O t _s c _s t _s g _s t _s g _s c _s c _s C _O G _O A _O C	
7	2168 (491 N-ras)	TGATGGCAAACAC ACA	CUR271 4 7A <u>108</u>	T _s G _s A _s T _s g _s g _s c _s a _s a _s a _s c _s a _s C _s A _s C _s A	63
			7B <u>109</u>	T _s G _s A _s T _s g _s g _s c _s a _s a _s a _s c _s a _s C _s A _s C _s a	
			7C <u>110</u>	T _O G _O A _O T _O g _s g _s c _s a _s a _s a _s c _s a _s C _O A O _C O _A	
8	2182	AGACTTGGTGTGT TG	CUR271 5 8A <u>111</u>	A _s G _s A _s C _s t _s t _s g _s g _s t _s g _s t _s G _s T _s T _s G	57
			8B <u>112</u>	A _s G _s A _s C _s t _s t _s g _s g _s t _s g _s t _s G _s T _s T _s g	
			8C <u>113</u>	A _O G _O A _O C _O t _s t _s g _s g _s t _s g _s t _s G _O T _O T _O G	
9	2383	GTCCTTCACCCGTT TG	CUR271 4 9A <u>114</u>	G _s T _s C _s C _s t _s t _s c _s a _s c _s c _s g _s T _s T _s T _s G	67
			9B <u>115</u>	G _s T _s C _s C _s t _s t _s c _s a _s c _s c _s g _s T _s T _s T _s G	
			9C <u>116</u>	G _O T _O C _O C _O t _s t _s c _s a _s c _s c _s g _s T _O T _O T _O g	
10	2393	CGTCATCCGAGTCC TT	CUR271 7 10A <u>117</u>	C _s G _s T _s C _s a _s t _s c _s c _s g _s a _s g _s t _s C _s C _s T _s T	66
			10B <u>118</u>	C _s G _s T _s C _s a _s t _s c _s c _s g _s a _s g _s t _s C _s C _s T _s t	

			10C <u>119</u>	C _O G _O T _O C _O a _s t _s c _s c _s g _s a _s g _s t _s C _O C _O T _O T	
11	2431	AGCCAGGTCACAC TTG	CUR271 8 11A <u>120</u>	A _s G _s C _s C _s a _s g _s g _s t _s c _s a _s c _s a _s C _s T _s T _s G	49
			11B <u>121</u>	A _s G _s C _s C _s a _s g _s g _s t _s c _s a _s c _s a _s C _s T _s T _s g	
			11C <u>122</u>	A _O G _O C _O C _O a _s g _s g _s t _s c _s a _s c _s a _s C _O T O _T O _G	
12	2453	GCCGAGATTCCAC AGT	CUR271 9 12A <u>123</u>	G _s C _s C _s G _s a _s g _s a _s t _s t _s c _s c _s a _s C _s A _s G _s T	77
			12B <u>124</u>	G _s C _s C _s G _s a _s g _s a _s t _s t _s c _s c _s a _s C _s A _s G _s t	
			12C <u>125</u>	G _O C _O C _O G _O a _s g _s a _s t _s t _s c _s c _s a _s C _O A O _G O _T	
13	3228 (629 K-ras)	CATCCTCCACTCCC TG	CUR272 0 13A <u>126</u>	C _s A _s T _s C _s c _s t _s c _s c _s a _s c _s t _s c _s C _s C _s T _s G	68
			13B <u>127</u>	C _s A _s T _s C _s c _s t _s c _s c _s a _s c _s t _s c _s C _s C _s T _s G	
			13C <u>128</u>	C _O A _O T _O C _O c _s t _s c _s c _s a _s c _s t _s c _s C _O C _O T _O g	
14	3253	ATCTCACGCACCAA CG	CUR272 1 14A <u>129</u>	A _s T _s C _s T _s c _s a _s c _s g _s c _s a _s c _s c _s A _s A _s C _s G	89
			14B <u>130</u>	A _s T _s C _s T _s c _s a _s c _s g _s c _s a _s c _s c _s A _s A _s C _s g	
			14C <u>131</u>	A _O T _O C _O T _O c _s a _s c _s g _s c _s a _s c _s c _s A _O A O _C O _G	
15	3506	TCCTCCTTCCGTCT GC	CUR272 2 15A <u>132</u>	T _s C _s C _s T _s c _s c _s t _s t _s c _s c _s g _s t _s C _s T _s G _s C	99
			15B <u>133</u>	T _s C _s C _s T _s c _s c _s t _s t _s c _s c _s g _s t _s C _s T _s G _s c	

			15C 134	T _O C _O C _O T _O c _s c _s t _s t _s c _s c _s g _s t _s C _O T _O G _O C	
16	1610	GGTCTCCTGCCCA CC			
17	1626	CGGGGTCCTCCTAC AG			
18	1642	TCAGGGGCCTGCG GCC			
19	1658	ATTCCGTCATCGCT CC			
20	1674	ACCACCACCAGCTT AT			
21	1690	CACACCGCCGGCG CCC			
22	1706	TCAGCGCACTCTTG CC			
23	1738	GTCCACAAAATGGT TC			
24	1754	TAGTGGGGTCGTAT TC			
25	2037	CGGTAGGAATCCTC TA			
26	2053	AATGACCACCTGCT TC			
27	2069	GGCACGTCTCCCA TC			
28	2085	TCCAGGATGTCCAA CA			
29	2101	CTCCTGGCCGGCGG TA			
30	2117	GCATGGCGCTGTAC TC			
31	2133	CGCATGTACTGGTC CC			
32	2149	GAAGCCCTCCCCG GTG			
33	2165	TGGCAAACACACA CAG			
34	2181	GACTTGGTGTGTT GA			
35	2197	GTGGATGTCCTCAA AA			

36	2213 Exon- exon	TCTGCTCCCTGTAC TG
37	2382	TCCTTCACCCGTTT GA
38	2398	GGGCACGTCATCC GAG
39	2414	TCCCCACCAGCACC AT
40	2430	GCCAGGTCACACTT GT
41	2446	TTCCACAGTGCGTG CA
42	2462	CCTGAGCCTGCCGA GA
43	2478	TAGCTTCGGGCGAG GT
44	2494	GATGTAGGGGATG CCG
45	2510	TCTTGGCCGAGGTC TC
46	2526 Exon- exon	TCCACTCCCTGCCG GG
47	3239	CGTGTAGAAGGCA TCC
48	3255	GGATCTCACGCACC AA
49	3271	CGCAGCTTGTGCTG CC
50	3287	AGGAGGGTTCAGC TTC
51	3303	CGGGGCCACTCTCA TC
52	3319	TTGCAGCTCATGCA GC
53	3335	TCAGGAGAGCACA CAC
54	3459	CTGAGCTTGTGCTG CG
55	3475	CCGGCACCTCCATG TC
56	3491	CACCTCCTTCCTGC

		AT
57	3507	CTCCTCCTTCCGTC TG
58	3523	CTTCCGTCCTTCCT TC
59	3539	CTTCCTTCCTTCCTT G
60	3555	CTGGGCTCCAGCA GCC
61	3571	CACGGTCCCGGGG TGA
62	3587	TGCAGTCACCTCGG CC
63	3603	CCTCCCTGGGAGG GTC
64	3619	GACAGTCTGTGCAC AG
65	3635	CATTGTTGGGATGTTC AA
66	3651	GCTGGGGTTCCGGT GG
67	3667	GGGAGGGGAGCTA AGG
68	3683	GGGCCACAGAGG CCT
69	3699	CATCTGTGCCCGAC AA
70	3715	TAATTTACTGTGAT CC
71	3731	TTCAAGACCATCC AA
72	1722	TGGATCAGCTGGAT GG
73	1690	CACACCGTCGGCG CCC
74	2101	CTCCAGGCCGGCG GTA

Please amend the paragraph on page 54, lines 6-7, as follows:

Compounds of particular interest are SEQ ID NOS 3A, 4A, 5A, 6A, 7A, 8A, 9A, 10A, 11A, 12A, 13A, 14A, 15A and 76A. 96, 99, 102, 105, 108, 111, 114, 117, 120, 123, 126, 129, 132 and 76.

Please amend Table 3 starting on page 58, as follows:

Table 3 Oligonucleotides prepared for the In vivo superiority and specificity analysis

Seq ID No	Clonon number/SEQ ID NO	Length and design	Sequence (Capital letters is β -D-oxy-LNA, s is phosphorothioate)
75	75D Cur2522* 75	16-mer fully thiolated	5'-t _s C _s C _s G _s t _s C _s a _s t _s C _s G _s C _s t _s C _s t _s C-3'
	75B Cur2524 135	16-mer LNA gapmer 3+3, fully thiolated	5'-t _s C _s C _s G _s t _s C _s a _s t _s C _s G _s C _s t _s C _s T _s C-3'
76A	76A Cur2525 76	16-mer, LNA gapmer 3+3, fully thiolated, 5 mismatches	5'-t _s C _s A _s G _s t _s a _s a _s t _s a _s G _s C _s C _s C _s A _s C-3'

* The benchmark oligonucleotide: ISIS 2503 n-4 i.e the ISIS 2503 oligonucleotide which is made 4 bp shorter.

Please amend Table 4 starting on page 60, as follows:

Table 4 LNA compounds as 16-mers and benchmark phosphorothioate as 20-mer

Seq ID No	Sequence (5'-3')	Internal number & seq design NO	Length and design
77	tccgtcatcgctcctcag gg	Cur 2119 77D	PS/DNA 20-mer
75 137	TCCGtcatcgctCCT C	Cur 2131 75A	β -D-oxy-LNA (captured letters)/DNA gapmer 16-mer full thiolated

Please amend Table 5 starting on page 62, as follows:

Table 5. Oligonucleotides containing alpha-L-oxy-LNA(capital letters and ^α) and beta-D-oxy-LNA (capital letters) used in the in vivo experiment. Residue c is methyl-c both for DNA and LNA, except for c DNA in 2713 and 2722.

Seq NO	ID	Internal ref & SeqID+ design NO	oligonucleotides	
75 <u>138</u>		2776 75F	T ^α _s C ^α _s C ^α _s g _s t _s c _s a _s t _s c _s g _s c _s t _s C ^α _s C ^α _s T ^α _s c	match
77 <u>139</u>		2778 77F	T ^α _s C ^α _s T ^α _s g _s t _s a _s a _s t _s a _s g _s c _s c _s C ^α _s C ^α _s C ^α _s c	Mismatch control
75 <u>140</u>		2742 75B	T _s C _s C _s g _s t _s c _s a _s t _s c _s g _s c _s t _s C _s C _s T _s c	match
77 <u>136</u>		2744 77B	T _s C _s T _s g _s t _s a _s a _s t _s a _s g _s c _s c _s C _s C _s C _s c	Mismatch control
6 <u>105</u>		2713 6A	C _s C _s C _s A _s t _s c _s t _s g _s t _s g _s c _s c _s C _s G _s A _s C	Match
15 <u>132</u>		2722 15A	T _s C _s C _s T _s c _s c _s t _s c _s c _s g _s t _s C _s T _s G _s C	Match